Toxicology of trans-1,4-Dichloro-2-butene
Review of Literature

Prepared for

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1.0 INTRODUCTION
1.1 Chemical Identification

*trans*-1,4-Dichloro-2-butene

\[
\begin{align*}
\text{Cl} & \quad \text{CH}_2 \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{H}_2\text{Cl}
\end{align*}
\]

*trans*-1,4-Dichloro-2-butene (C_4H_6Cl_2, CASRN 110-57-6, mol. wt. = 125.00) is also called:

- 2-Butene, 1,4-dichloro-, \((E)\)- (8CI9CI)
- 2-Butene, 1,4-dichloro-, *trans*-
- 2-Butylene dichloride
- 1,4-Dichloro-2-butene
- 1,4-Dichlorobutene-2, *trans*-
- 1,4-Dichloro-*trans*-2-butene
- *trans*-1,4-Dichlorobutene

1.2 Physical-Chemical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Point, °C</td>
<td>1-3</td>
<td>Weast and Astle (1980)</td>
</tr>
<tr>
<td>Boiling Point, °C</td>
<td>155.5</td>
<td>Weast and Astle (1980)</td>
</tr>
<tr>
<td>Density at 20 °/4°C</td>
<td>1.183</td>
<td>Weast and Astle (1980)</td>
</tr>
</tbody>
</table>
### TOXICOLOGICAL SUMMARY OF *trans*-1,4-DICHLORO-2-BUTENE

01/14/97

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ethanol, diethyl ether, acetone, and benzene</td>
<td></td>
</tr>
</tbody>
</table>
2.0 PRODUCTION PROCESS ANALYSIS

Butadiene can be converted to *trans*-1,4-dichloro-2-butene (DCB) via a four-step process. In step one, a mixture of DCB and 3,4-dichloro-1-butene is produced as a result of vapor-phase chlorination of butadiene (SRI Int., 1996). An equilibrium results when the mixture is heated. The residue resulting from removal of 3,4-dichloro-1-butene, which has a lower boiling point, is normally used without further separation (IARC, 1977).
3.0 PRODUCTION AND IMPORT VOLUMES


In the US, DCB has been used primarily as an intermediate in the manufacture of hexamethylenediamine and chloroprene. While U.S. production of hexamethylenediamine and polychloroprene rubber (neoprene) (the end-product from chloroprene) in 1975 was 340,000 and 143,900 metric tons (Mg), respectively, the percent originally derived from DCB was not known (Fishbein, 1979).

Two U.S. companies were reported by IARC (1977) as manufacturers of DCB. However, for 1977, E.I. DuPont de Nemours & Co. was the only manufacturer of DCB which reported production levels (between 100 to 500 million pounds per year; 45,000 to 226,800 Mg/year) to the U.S. EPA (TSCAPP, 1983). More recent data are not available.

Import data were not located.
4.0 USES

In the U.S., DCB has been used as an intermediate in the manufacture of hexamethylenediamine and chloroprene since 1951 (U.S. Tariff Commission, 1964; cited by IARC, 1977). Hexamethylenediamine is used as a chemical intermediate in the production of nylon 66 and 612 polyamide resins; chloroprene is used in the production of polychloroprene (neoprene) rubber (Fishbein, 1979).

DCB is also used as a U.S. EPA RCRA Appendix VIII supplementary analytical standard (Tomkins et al., 1989).
5.0 ENVIRONMENTAL OCCURRENCE

5.1 Occurrence

DCB is not known to occur naturally (IARC, 1977).

5.2 Persistence

Hermens et al. (1985) calculated a hydrolysis rate constant \( k \) for DCB in a 1:1 acetone-water mixture using the equation

\[
k = \frac{-1}{t} \ln\left(\frac{(H_3O^+)_t}{(H_3O^+)_4}\right)
\]

where \((H_3O^+)_t\) is the concentration of liberated \((H_3O^+)\) at time \( t \), and \((H_3O^+)_4\) is the concentration of liberated \((H_3O^+)\) after complete hydrolysis. With a reaction time \( t \) of 5 days, \( \log k = -5.09 \) (min\(^{-1}\)), while with a reaction time of 10 days, \( \log k = -5.01 \) (min\(^{-1}\)). Based on these rate constants, the half-life \( (t_{1/2}) \) of DCB in the acetone-water mixture was calculated to be 13 hours \( (t_{1/2} = 1.155 \times 10^2/k) \).
6.0 HUMAN EXPOSURE

Occupational exposure to DCB may occur during its production or during its use as an intermediate in the manufacture of hexamethylenediamine and chloroprene (Fishbein, 1979). RTECS (1996) did not report on any occupational surveys conducted by the National Institute for Occupational Safety and Health (NIOSH).

No data on non-occupational exposures were found.
7.0 REGULATORY STATUS

REGULATIONS

<table>
<thead>
<tr>
<th>EPA Regulatory Action</th>
<th>Effect of Regulation/Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 CFR 60C Standards of Performance for New Stationary Sources; Volatile Organic Compound (VOC) Emissions From the Synthetic Organic Chemical Manufacturing Industry (SOCMI). Subpart NNNC Distillation Operations. Subpart RRRC Reactor Processes.</td>
<td>These standards implement section 111 of the Clean Air Act (CAA), and requires all new, modified, and reconstructed SOCMI distillation and reactor process facilities to achieve an emission reduction that reflects the capabilities of the best demonstrated system of continuous emission reduction, considering costs, nonair quality health and environmental impacts and energy requirements. The chemicals (including DCB) affected for distillation operations are listed in 60.667 and those affected for reactor processes are listed in 60.707.</td>
</tr>
<tr>
<td>40 CFR 63C National Emission Standards for Hazardous Air Pollutants for Source Categories.</td>
<td>Plants manufacturing DCB as a primary product whose emissions contain at least 10 tons per yr, or DCB in combination with another listed compound in amounts of at least 25 tons/yr must report their annual emissions to EPA. DCB is listed in Table 1 to Subpart FCSynthetic Organic Chemical Manufacturing Industry Chemicals.</td>
</tr>
<tr>
<td>40 CFR 258C Criteria for Municipal Solid Waste Landfills (MSLF)</td>
<td>Section 54 of CFR 258 requires detection monitoring at MSLF units for DCB.</td>
</tr>
<tr>
<td>40 CFR 264C CRA. Appendix IXC Ground water monitoring list.</td>
<td>Lists DCB as one of the chemical substances for which suitable analytical methods are available for monitoring groundwater contamination at hazardous waste sites.</td>
</tr>
<tr>
<td>40 CFR 268C CRA. Appendix III</td>
<td>Lists chemical substances, including DCB, regulated under 40 CFR 268.32 (land disposal prohibition; California list).</td>
</tr>
</tbody>
</table>
8.0  TOXICOLOGICAL DATA

**Summary:** The metabolic fate of DCB is not known. It may be metabolized to an epoxide which would structurally be a $\beta$-chloro ether. In rats, the oral LD$_{50}$ is 89 mg/kg body weight (710 $\mu$mol/kg bw) while the 30-minute inhalation LC$_{50}$ is 784 ppm (4000 mg/m$^3$; 32100 Fmol/m$^3$). In rats exposed to 62 ppm (320 mg/m$^3$; 2500 Fmol/m$^3$) DCB by inhalation for 4 hours, mortality occurred in 2/6 animals after 14 days. No short-term, chronic, or reproductive studies are available.

In a carcinogenicity study, DCB was evaluated for its potential to induce tumors in female ICR/Ha Swiss mice when administered by skin painting, or by intraperitoneal (i.p.) or subcutaneous (s.c.) injection. No tumors were observed when DCB was administered at 1.0 mg (8.0 $\mu$mol) in 0.1 mL acetone to the shaved dorsal skin, 3 times per week for 77 weeks. The tumor response was also not significantly increased in these mice when DCB was injected i.p. at 0.05 mg (0.4 $\mu$mol) in 0.05 mL tricaprylin once per week for 77 weeks. However, when administered by s.c. injection once per week for 77 weeks, this dose induced a significant increase in the incidence of sarcomas at the site of injection. In a 2-stage carcinogenicity bioassay, DCB was negative as an initiator when administered once at 1 mg (8 $\mu$mol) in 0.1 mL acetone to the shaved skin of 6- to 8-week-old female ICR/Ha Swiss mice skin, followed 14 days later with phorbol myristate acetate (2.5 $\mu$g/0.1 mL acetone) applied 3 times per week for 77 weeks.

DCB has been evaluated for genotoxicity in only a limited number of prokaryotic test systems. DCB was reported to induce gene mutations in *Salmonella typhimurium* in the absence or presence of active rat and human liver S9, and in *Escherichia coli* in the presence or absence of rat liver metabolic activation.

8.1  Human Data

No human data were found.

8.2  General Toxicology

8.2.1  Chemical Disposition, Metabolism, and Toxicokinetics

DCB may be metabolized to an epoxide which would structurally be a $\beta$-chloro ether (Van Duuren et al., 1975).
8.2.2 Acute Exposures

The studies described in this section are presented in Table 8-1.

8.2.2.1 Oral Administration

The oral LD$_{50}$ of DCB in rats (age, strain, and sex not provided) was reported to be 89 mg/kg body weight (710 mol/kg bw) (Smith et al., 1951; cited by IARC, 1977).

8.2.2.2 Inhalation Exposure

In rats (age, strain, and sex not specified) administration of 62 ppm (weight/vol)(320 mg/m$^3$; 2500 Fmol/m$^3$) DCB by inhalation for 4 hours caused mortality in 2/6 animals after 14 days (Smith et al., 1951; cited by IARC, 1977).

In an 8(e) submission by DuPont Chemical Co. (1974) for the Toxic Substances Control Act (TSCA), the acute inhalation toxicity of DCB in rats was evaluated. Young adult ChR-CD male rats (252-277 g)(6 per dose group) were exposed to DCB (1.43% cis-isomer; 97.17% trans-isomer) at 240, 370, 410, 440, 540, 760, or 3600 ppm (vol/vol) (1200 to 18000 mg/m$^3$; 9800 to 150000 Fmol/m$^3$) for 30 minutes. Gross and histopathologic examinations were performed on 2 rats per dose group at 7 days post-exposure (exposure information not provided) and on 1 rat exposed to 760 ppm and found dead at 13 days post-exposure. All other animals were observed for 14 days post-exposure.

The 30-minute LC$_{50}$ was 784 ppm (4000 mg/m$^3$; 32100 Fmol/m$^3$). With the 760 ppm-dose (3900 mg/m$^3$; 31000 Fmol/m$^3$), destruction of the air passage,
kidney damage, testicular atrophy, and hypoplastic bone marrow occurred. The latter two changes were interpreted as a reflection of stress and emaciation and were considered not to be compound-related. Examination of other tissues (lymph nodes, stomach, duodenum, epididymis, thyroid, adrenal glands, brain, and eyes) revealed no compound-related effects. Exposure of rats to 410 ppm (2100 mg/m$^3$; 17000 Fmol/m$^3$) resulted in damage to the tracheobronchial epithelium.

8.2.3 Short-term and Subchronic Exposures

No data were found.

8.2.4 Chronic Exposures

No data were found.

8.2.5 Reproductive Effects

No data were found.

8.2.6 Carcinogenicity

The studies described in this section are presented in Table 8-2.

8.2.6.1 Dermal Application

No tumors were detected in female ICR/Ha Swiss mice administered 1.0 mg (8.0 :mol) DCB in 0.1 mL acetone on the shaved dorsal skin, 3 times per week for 77 weeks, beginning at 6 to 8 weeks of age (Van Duuren et al., 1975).
8.2.6.2 Subcutaneous Injection

There was a significant increase in the incidence of sarcomas at the site of injection when DCB at 0.05 mg (0.4 \text{ :mol}) in 0.05 mL tricaprylin was administered once per week for 77 weeks into the left flank of female ICR/Ha Swiss mice beginning at 6 to 8 weeks of age (Van Duuren et al., 1975).

8.2.6.3 Intraperitoneal Injection

A significant increase in tumor incidence was not detected in female ICR/Ha Swiss mice administered DCB at 0.05 mg (0.4 \text{ :mol}) in 0.05 mL tricaprylin by i.p. injection, once per week for 77 weeks, beginning at 6 to 8 weeks of age (Van Duuren et al., 1975). In a review of this study, IARC (1977) commented on the low dose used.

8.2.6.4 Initiation/Promotion Studies

In a 2-stage carcinogenicity study, DCB was negative as an initiator when applied as a single dose of 1 mg (8 \text{ :mol}) DCB in 0.1 mL acetone to the skin of 6- to 8-week-old female ICR/Ha Swiss mice (Van Duuren et al., 1975). This application was followed 14 days later with 2.5 \text{ :g phorbol myristate acetate in 0.1 mL acetone, applied to the skin 3 times per week for 77 weeks.}

8.3 Genetic Toxicology

Genotoxicity studies with DCB are summarized in Table 8-3.

Using the plate incorporation assay, DCB (76.8\% trans/21.6\% cis-isomer) at 10 to 1000 FM (7.7 to 768 FM \text{ trans-isomer}) induced a significant increase in \text{his} gene mutations in \text{S. typhimurium strain TA100} in the presence of mouse or
human liver S9 fractions with or without a NADPH-generating system (Bartsch et al., 1979). At 1000 FM, a 9-fold and a 5- to 6-fold increase in revertants over controls was observed with or without mouse S9 metabolic activation, respectively. DCB was 64% less mutagenic in the presence of active human liver S9 than when metabolically activated by mouse liver S9.

DCB is also reported to induce mutations in E. coli (Mukai and Hawryluk, 1973Abst.). Experimental details were not provided.

8.4 Immunotoxicity

No data were found.
<table>
<thead>
<tr>
<th>Age, Strain, Species</th>
<th>Exposed Animals</th>
<th>Control Animals</th>
<th>Chemical Form, Purity</th>
<th>Dose</th>
<th>Exposure Duration; Observation Period</th>
<th>Mortality</th>
<th>Results/Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2.2.1 Oral Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male (age not given)</td>
<td>n.g.</td>
<td>n.g.</td>
<td>trans-DCB, purity not specified</td>
<td>n.g.</td>
<td>LD$_{50}$ = 89 mg/kg bw (710 mol/kg bw)</td>
<td>No details were given.</td>
<td>Smith et al. (1951; cited by IARC, 1977)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.2.2 Inhalation Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>6M per dose</td>
</tr>
<tr>
<td>252-97.17% trans-isomer, 97.17% trans-isomer)</td>
</tr>
<tr>
<td>240, 370, 410, 440, 540, 760, or 3600 ppm (vol/vol)$^3$ (1200 to 18000 mg/m$^3$; 9800 to 150000 Fmol/m$^3$)</td>
</tr>
<tr>
<td>Age, Strain, Species</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: n.g. = not given; M = male.

* exposure lasted 30 min unless all rats died sooner. Gross and histopathologic examinations were performed on 2 rats surviving exposure for 7 days, on 1 rat found dead after 13 recovery days. ² duplicate; ³ lymph nodes, stomach, duodenum, epididymis, thyroid, adrenal glands, brain, and eyes


### Carcinogenicity of trans-1,4-Dichloro-2-butene

<table>
<thead>
<tr>
<th>Age, Strain, Species</th>
<th>Exposed Animals</th>
<th>Control Animals</th>
<th>Chemical Form, Purity</th>
<th>Dose</th>
<th>Exposure Duration</th>
<th>Mortality</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6.1 Dermal Application</td>
<td>30F</td>
<td>30F (acetone)</td>
<td>trans-DCB, purity not specified</td>
<td>1.0 mg /0.1 mL acetone (8.0 mol/0.1 mL) applied to shaved dorsal skin, 3 times/wk</td>
<td>77 weeks</td>
<td>Mean survival time in treated mice not decreased as compared to controls</td>
<td>Complete necropsies, except for cranial region, were performed on all mice. No tumors were detected in DCB-treated mice.</td>
<td>Van Duuren et al. (1975)</td>
</tr>
<tr>
<td>- to 8-wk-old ICR/Ha wiss mice</td>
<td>85F (no treatment)</td>
<td>30F</td>
<td>85F (no treatment)</td>
<td>trans-DCB, purity not specified</td>
<td>77 weeks</td>
<td>Mean survival time in treated mice not decreased as compared to controls</td>
<td>Complete necropsies, except for cranial region, were performed on all mice.</td>
<td>Van Duuren et al. (1975)</td>
</tr>
<tr>
<td>2.6.2 Subcutaneous Injection</td>
<td>30F</td>
<td>50F (tricaprylin)</td>
<td>trans-DCB, purity not specified</td>
<td>0.05 mg/0.05 mL tricaprylin (0.40 mol/0.05 mL) injected s.c. into left flank, once/wk</td>
<td>77 weeks</td>
<td>Mean survival time in treated mice not decreased as compared to controls</td>
<td>Complete necropsies, except for cranial region, were performed on all mice. Injection Site: There was a significant increase in the incidence of sarcomas at the injection site in treated mice (3/30 vs. 0/50 tricaprylin controls and 0/85 untreated controls).</td>
<td>Van Duuren et al. (1975)</td>
</tr>
<tr>
<td>- to 8-wk-old ICR/Ha wiss mice</td>
<td>85F (no treatment)</td>
<td>30F</td>
<td>85F (no treatment)</td>
<td>trans-DCB, purity not specified</td>
<td>77 weeks</td>
<td>Mean survival time of treated mice was decreased as compared to tricaprylin controls (478 days vs. 513 days, respectively).</td>
<td>Complete necropsies, except for cranial region, were performed on all mice. There was no significant increase in tumor incidence in treated mice as compared to controls. In a review of this study, IARC (1977) noted the low dose used.</td>
<td>Van Duuren et al. (1975)</td>
</tr>
<tr>
<td>2.6.3 Intraperitoneal Injection</td>
<td>30F</td>
<td>30F (tricaprylin)</td>
<td>trans-DCB, purity not specified</td>
<td>0.05 mg/0.05 mL tricaprylin (0.40 mol/0.05 mL) injected i.p., once/wk</td>
<td>77 weeks</td>
<td>Mean survival time of treated mice was decreased as compared to tricaprylin controls (478 days vs. 513 days, respectively).</td>
<td>Complete necropsies, except for cranial region, were performed on all mice. There was no significant increase in tumor incidence in treated mice as compared to controls.</td>
<td>Van Duuren et al. (1975)</td>
</tr>
<tr>
<td>- to 8-wk-old ICR/Ha wiss mice</td>
<td>85F (no treatment)</td>
<td>30F</td>
<td>85F (no treatment)</td>
<td>trans-DCB, purity not specified</td>
<td>77 weeks</td>
<td>Mean survival time for groups 1, 2, 3, and 4 were 478, 526, 460, and 510 days, respectively.</td>
<td>Complete necropsies, except for cranial region, were performed on all mice. There was no significant increase in tumor incidence in mice treated with trans-DCB + PMA as compared to controls.</td>
<td>Van Duuren et al. (1975)</td>
</tr>
<tr>
<td>2.6.4 Initiation/Promotion Studies</td>
<td>30F (trans-DCB + PMA)</td>
<td>30F (trans-DCB + acetone)</td>
<td>trans-DCB, purity not specified</td>
<td>one application of 1 mg (8 mol) trans-DCB in 0.1 mL acetone on skin; followed 14 days later with 2.5 g PMA/0.1 mL acetone, applied to skin 3 times/wk</td>
<td>77 weeks</td>
<td>Mean survival time for groups 1, 2, 3, and 4 were 478, 526, 460, and 510 days, respectively.</td>
<td>Complete necropsies, except for cranial region, were performed on all mice. There was no significant increase in tumor incidence in mice treated with trans-DCB + PMA as compared to controls.</td>
<td>Van Duuren et al. (1975)</td>
</tr>
</tbody>
</table>

Abbreviations: PMA = phorbol myristate acetate; F = female; i.p. = intraperitoneal; s.c. = subcutaneous
## Table 8-3. Genotoxicity of trans-1,4-Dichloro-2-butene

<table>
<thead>
<tr>
<th>Test System</th>
<th>Biological Endpoint</th>
<th>S9 Metabolic Activation</th>
<th>Purity</th>
<th>Doses Used</th>
<th>Endpoint Response</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella typhimurium strain A100</td>
<td><em>his</em> gene mutations (plate incorporation method)</td>
<td>+/- active mouse or human liver S9 (activity based on presence or absence of a NADP generating system)</td>
<td>76.8% trans/21.6% cis.</td>
<td>10 to 1000 FM (7.7 to 768 FM trans-isomer)</td>
<td>positive/positive</td>
<td>At 1000 FM, a 9-fold and a 5- to 6-fold increase in revertants over controls was observed with or without mouse S9 metabolic activation, respectively. DCB was 64% less mutagenic in the presence of active human liver S9 than when metabolically activated by mouse liver S9.</td>
<td>Bartsch et al. (1979)</td>
</tr>
<tr>
<td>Escherichia coli (strain not provided)</td>
<td>gene mutations (locus not provided)</td>
<td>details not provided</td>
<td>n.p.</td>
<td>n.g.</td>
<td>positive</td>
<td>No experimental details were given.</td>
<td>Mukai and Hawryluk (1973Asbt.)</td>
</tr>
</tbody>
</table>

Abbreviations: n.p. = not provided; n.g. = not given.
9.0 STRUCTURE-ACTIVITY RELATIONSHIPS

No data were found.
10.0 COMPLEX MIXTURES

Summary: The hepatotoxicity and nephrotoxicity of a complex waste mixture containing DCB (59 mg [470 Fmol]/g) were evaluated in rats. Centrilobular necrosis of the liver was detected in some rats treated with 1.0 or 5.0 mg waste mixture/kg (DCB = 0.059 or 0.30 mg/kg, respectively; 0.47 or 2.4 Fmols/kg, respectively). The relative liver weight, hepatic water content, and relative and absolute kidney weights for the treated groups were also increased. In addition, serum activities of alkaline phosphatase, lactate dehydrogenase, and ornithine carbamyl transferase, and the serum concentration of total bilirubin (all indicators of hepatic injury), as well as the serum concentration of urea nitrogen, were increased.

The same complex waste mixture containing DCB at 59 mg (470 Fmol)/g induced gene mutations in S. typhimurium TA100 at 0.1 to 2.0 Fg crude waste (DCB at 6-120 x 10^{-3} Fg; 0.05-0.9 x 10^{-3} Fmols/plate in the presence and absence of rat liver S9 using the plate incorporation method. The same waste mixture induced lambda prophage in E. coli. The lowest effective dose (LED) for the complex mixture in the presence of S9 was 50 x 10^{-6} Fg/mL (DCB at 3 x 10^{-6} Fg/mL; 2 x 10^{-5} FM), while in the absence of S9 it was 2 x 10^{-7} Fg/mL (DCB at 1.2 x 10^{-8} Fg/mL; 9 x 10^{-8} FM). The maximal response was a 26-fold increase with metabolic activation versus a 5-fold increase without S9.

10.1 In Vivo Acute Toxicity

Studies described in this section are presented in Table 10-1. Simmons et al. (1988; see also Simmons and Berman, 1989) evaluated the hepatotoxicity of a waste sample containing DCB at 59 mg/g (470 Fmol/g) (see Table 10-1 for list of other chemicals detected in the sample). Male Fischer 344 rats (65 days of age) were administered a single dose of 1.0 or 5.0 mg waste sample/kg (0.06 or 0.3 mg DCB/kg; 0.5 or 2.4 Fmol DCB/kg) by gavage and were sacrificed 24 hours later. All high-dose rats died before the end of the study and could not be evaluated. A Marked @ centrilobular necrosis was detected in the livers of 4/5 low-dose rats (vs. 0/24 controls), while the liver of the remaining rat exhibited moderate (i.e., less severe than marked) centrilobular necrosis (vs. 0/24 controls). Relative liver weight (liver-to-body weight ratio) and hepatic water content (wet-to-dry-weight ratio) were significantly increased in low-dose rats. These rats also had significantly increased serum activities of several indicators of hepatic injury;
alkaline phosphatase, lactate dehydrogenase, ornithine carbamyl transferase, and
total bilirubin.

In a further analysis of the study by Simmons et al. (1988), Simmons et al. (1995) evaluated the nephrotoxicity of the waste sample in the same rats. A description of renal histopathology was not given, but it was noted that relative and absolute kidney weights were significantly increased in the low-dose rats. The serum concentration of urea nitrogen (BUN), but not of creatinine (CREAT), was also significantly increased in these rats. The authors noted that serum BUN is not notably sensitive to low levels of renal damage, suggesting that the renal damage must have been moderate to severe.

10.2 Genetic Toxicology: Prokaryotic Mutagenesis

Studies described in this section are presented in Table 10-2.

DeMarini et al. (1987) reported that a crude petrochemical waste containing DCB at 59 mg (470 Fmol)/g waste as well as a dichloromethane waste extract (concentration of DCB not determined) induced mutations in S. typhimurium strain TA100. Doses tested were 0.1 to 2.0 Fg crude waste/plate (DCB at 6 - 120 x 10^{-3} Fg/plate; 0.05 - 0.9 x 10^{-3} Fmol/plate), or waste extract in the presence and absence of metabolic activation using the plate incorporation method with strain TA100. The crude waste led to an approximate 3 fold higher response than the waste extract.

Houk and DeMarini (1988) reported that the same crude petrochemical waste induced lambda prophage in E. coli strain WP2s(8) using the microscreen assay. The doses tested were 5 x 10^{-5} to 400 Fg crude waste/mL (DCB at 3 x 10^{-6} to 20 Fg/mL; 2.4 x 10^{-5} to 200 FM) in the presence of rat liver S9 and 2 to 15 x 10^{-7} Fg crude waste/mL (DCB at 1.2 - 9 x 10^{-8} Fg/mL; 9 - 71 x 10^{-8} FM) in the absence of S9. The lowest effective dose (LED) in the presence of S9 was 50 x 10^{-6} Fg crude waste/mL (DCB at 3 x 10^{-6} Fg/mL; 2 x 10^{-5} FM), while without
metabolic activation it was $2 \times 10^{-7}$ Fg crude waste/mL (DCB at $1.2 \times 10^{-8}$ Fg/mL; $9 \times 10^{-8}$ FM). The maximal response was a 26-fold increase with S9 at $1.5$ Fg crude waste/mL (DCB at $9 \times 10^{-2}$ Fg/mL; $0.7$ FM) vs. a 5-fold increase without S9 at $8 \times 10^{-7}$ Fg crude waste/mL (DCB at $5 \times 10^{-8}$ Fg/mL; $4 \times 10^{-7}$ FM).
<table>
<thead>
<tr>
<th>Age, Strain, Species</th>
<th>Exposed Animals</th>
<th>Control Animals</th>
<th>Chemical Mixture Dose</th>
<th>Exposure Duration</th>
<th>Mortality</th>
<th>Results/Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>trans-DCB (59 mg/g [470 mol/g]), cis-1,4-DCB (18 mg/g), benzyl chloride (3 mg/g), carbon tetrachloride (68 mg/g), chloroform (2.9 mg/g), hexachloroethane (0.6 mg/g), methylene chloride (21 mg/g), naphthalene (&lt; 0.1 mg/g), tetrachloroethylene (11 mg/g), toluene (240 mg/g), trichloroethylene (4 mg/g), 1,1,1-trichloroethane (&lt; 0.1 mg/g), water (1.8%), metals ([concentrations in g/g] antimony [&lt; 12], arsenic [&lt; 24], barium [&lt; 7], beryllium [&lt; 2], cadmium [&lt; 5], chromium [&lt; 5], lead [&lt; 19], mercury [&lt; 22], nickel [68], selenium [&lt; 470], silver [&lt; 3], thallium [&lt; 23])</td>
<td>single dose</td>
<td>1/6 LD and 6/6 HD rats died within 24 h of dosing; none of the controls died</td>
<td>Simmons et al. (1988); Simmons and Berman (1989); Simmons et al. (1995)</td>
<td></td>
</tr>
</tbody>
</table>

| Abbreviations: M = male; LD = low dose; HD = high dose. | | | | | | | |

|Organ Weight:| Relative liver weight (liver-to-body weight ratio x 100) was significantly increased in LD rats (4.65 "0.08 vs. 3.35 "0.11 in controls; absolute weights not given). Relative and absolute kidney weights were significantly increased in LD rats (relative wt: 0.93 "0.07 vs. 0.76 "0.02 in controls; absolute wt: 2.00 "0.22 vs. 1.67 "0.03 in controls). |

|Organ Water Content:| Hepatic water content (wt-to-dry-weight ratio) was significantly increased in LD rats (4.02 "0.34 vs. 3.49 "0.07 in controls). Renal water content was not given. |

|Serum Indicators of Hepatic Injury:| The serum activities of alkaline phosphatase, lactate dehydrogenase, and ornithine carbamyl transferase, and the serum concentration of total bilirubin were significantly increased in LD rats as compared to controls. |

<p>|Serum Indicators of Renal Injury:| The serum concentration of urea nitrogen (BUN) but not of creatinine (CREAT) was significantly increased in LD rats as compared to controls. Simmons et al. (1995) noted that serum BUN is Anot notably sensitive to low levels of renal damage, @, suggesting that the renal damage must have been moderate to severe. |</p>
<table>
<thead>
<tr>
<th>Test System</th>
<th>Biological Endpoint</th>
<th>S9 Metabolic Activation</th>
<th>Purity</th>
<th>Dose</th>
<th>Endpoint Response</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. typhimurium train TA100</td>
<td>his reverse gene mutations (plate incorporation method)</td>
<td>+/-</td>
<td>59 mg DCB/g (470 Fmol/g) petrochemical waste.</td>
<td>0.1 to 2.0 Fg crude waste or waste extract/plate (6 - 120 x 10^{-3} Fg DCB/plate; 0.05 - 0.9 x 10^{-3} Fmol DCB/plate)</td>
<td>positive/positive</td>
<td>Both the crude waste and the dichloromethane extracted waste induced positive dose responses.</td>
<td>DeMarini et al. (1987)</td>
</tr>
<tr>
<td>E. coli strain WP2s(8)</td>
<td>lambda prophage induction (microscreen assay)</td>
<td>+/-</td>
<td>59 mg DCB/g (470 Fmol/g) petrochemical waste.</td>
<td>+S9 = 5 x 10^{-5} to 400 Fg waste/mL (3 x 10^{-6} to 20 Fg DCB/mL; 2.4 x 10^{-5} to 200 Fmol DCB) vs. -S9 LED = 2 x 10^{-7} Fg/mL (1.2 x 10^{-8} Fg DCB/mL; 0.09 x 10^{-6} Fmol DCB)</td>
<td>positive/positive</td>
<td>S9 reduced the genotoxic potency of the waste; +S9 LED = 50x10^{-6} Fg/mL (3 x 10^{-6} Fg DCB/mL; 2 x 10^{-5} Fmol DCB) vs. -S9 LED = 2 x 10^{-7} Fg/mL (1.2 x 10^{-8} Fg DCB/mL; 0.09 x 10^{-6} Fmol DCB) while the maximal response was a 26-fold increase with S9 at 1.5 Fg/mL (9 x 10^{-2} Fg DCB/mL; 0.7 FM DCB) vs. a 5-fold increase without S9 at 8 x 10^{-7} Fg/mL (5 x 10^{-8} Fg DCB/mL; 4 x 10^{-7} FM DCB).</td>
<td>Houk and DeMarini (1988)</td>
</tr>
</tbody>
</table>

Abbreviations: LED = lowest effective dose.
11.0 ONLINE DATABASES AND SECONDARY REFERENCES SEARCHED

11.1 Online Databases

Chemical Information System Files

ISHOW (Information System for Hazardous Organics in Water)
SANSS (Structure and Nomenclature Search System)
TSCAPP (Toxic Substances Control Act Plant and Production)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

359 Chemical Economics Handbook

Internet Databases


National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)
TRI (Toxics Release Inventory; compounds listed in the SARA 313 list [40 CFR 372])

STN International Files

BIOSIS (Biological Abstracts)
CA File (Chemical Abstracts)
CANCERLIT
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)
HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)
MEDLINE (Index Medicus)
RTECS (Registry of Toxic Effects of Chemical Substances)
TOXLINE
TOXLIT
TOXICOLOGICAL SUMMARY OF trans-1,4-DICHLORO-2-BUTENE

TOXLINE includes the following subfiles, which often have only the toxicology information from the databases named:

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<thead>
<tr>
<th>Toxicity Bibliography</th>
<th>TOXBIB</th>
</tr>
</thead>
<tbody>
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<td>CIS</td>
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<td>Hazardous Materials Technical Center</td>
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<td>Environmental Mutagen Information Center File</td>
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<td>Environmental Teratology Information Center File (continued after 1989 by DART)</td>
<td>ETIC</td>
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<tr>
<td>Toxicology Document and Data Depository</td>
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<td>FEDRIP</td>
</tr>
</tbody>
</table>

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11.2 Secondary References Used


11-2
Listed in Section 12.

12.0 REFERENCES


DuPont Chemical Co. 1974. Initial Submission: Acute Inhalation Toxicity of cis- and trans-1,4-Dichlorobutene-2 (1.43% cis-1,4-DCB, 97.1% trans-1,4-DCB) in Rats, with Cover Letter Dated 10/15/92. U.S. EPA/OTS Public Files, Document Number 88-920009575. Fiche Number 0571232.


Simmons, J.E., R.S.H. Yang, and E. Berman. 1995. Evaluation of the Nephrotoxicity of Complex


